# TECHNICAL COMMENTARY

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## Treatments for relapse prevention

### Introduction

Studies have shown that about 80% of patients relapse to psychosis within 5 years of initial diagnosis. Antipsychotic drugs have played a central role in the treatment of schizophrenia for more than 50 years and antipsychotic use significantly reduces the risk of relapse.

### Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

### Results

We found 12 reviews that met our inclusion criteria[3-14].

- High quality evidence shows a small benefit of specialist first-episode psychosis programs (involving both psychosocial and pharmaceutical treatments) for reducing the risk of relapse and less all-cause discontinuation of treatment compared to treatment as usual. These programs may also reduce the length of hospital stay should relapse occur.
- Moderate quality evidence suggests relapse and rehospitalisation rates were higher after discontinuation of antipsychotics in people in remission following a first-episode of psychosis. Relapse rates were highest in studies with a short follow-up (<1 year) a non-targeted or non-intermittent discontinuation strategy, a lower relapse threshold, a smaller sample size, and in



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samples of patients with drug or alcohol dependency.

- Moderate to high quality evidence finds gradual tapering off antipsychotics over 3 months after remittance of a first-episode of psychosis results in fewer relapses for up to 2 years than abrupt discontinuation. However, tapering results in more adverse effects.
- Moderate to high quality evidence suggests a medium-sized effect of reduced risk of relapse in people receiving antipsychotics, particularly clozapine, although antipsychotics resulted in more weight gain, movement disorders and sedation than placebo. Long-acting injectable antipsychotics may be more effective than oral antipsychotics, second-generation antipsychotics may be more effective than first-generation antipsychotics, and continuous antipsychotic use may be more effective than intermittent antipsychotic use.
- Moderate quality evidence suggests a small to medium-sized effect of reduced risk of relapse in people receiving standard dose antipsychotics compared to people receiving very low dose antipsychotics (< 50% of daily defined dose), although standard dose antipsychotics resulted in more people dropping out of trials due to side effects. No differences were reported in relapses or side effects when low dose (50 to < 100% of daily defined dose) was compared to standard dose.



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*Alvarez-Jimenez M, Parker AG, Hetrick SE, McGorry PD, Gleeson JF*

## Preventing the Second Episode: A Systematic Review and Meta-analysis of Psychosocial and Pharmacological Trials in First-Episode Psychosis

**Schizophrenia Bulletin 2011; 37(3): 619-630**

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| **Comparison 1** | **Specialist first-episode psychosis (FEP) programs (comprising multidisciplinary teams administering unspecified low-dose atypical antipsychotics, manualised cognitive-behavioural strategies, individualised management plans and counselling and psychoeducation), vs. treatment as usual (comprising usual care from non-specialist mental health services).** |
| **Summary of evidence** | **High quality evidence (large sample, consistent, precise, direct) suggests specialist FEP programs reduce the risk of relapse compared to treatment as usual. Moderate to high quality evidence (unable to assess precision) suggests specialist FEP programs reduce the length of hospital stay following relapse.** |
| **Relapse rate** | |
| *Small effect size favouring FEP programs for preventing relapse;*<br>3 RCTs, N = 679, OR = 1.80, 95%CI 1.31 to 2.48, $p < 0.001$, $I^2 = 0\%$, $p = 0.82$<br>The number needed to treat (NNTB for the FEP programs to prevent one relapse was approximately 8. | |
| **Days in hospital** | |
| *The number of days in hospital following relapse was lower with specialist treatment;*<br>3 RCTs, N = 402, WMD = -26.20, 95%CI -7.35 to -45.06, $p < 0.01$, $I^2 = 0\%$, $p = 0.71$ | |
| **Consistency in results**‡ | Consistent |
| **Precision in results**§ | Precise for relapse, unable to assess days in hospital (measure not standardised). |
| **Directness of results**‖ | Direct |
| **Comparison 2** | **First generation antipsychotic (FGA) medications (various) vs. placebo for reducing relapse rate.** |

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| **Summary of evidence** | **Moderate quality evidence (consistent, imprecise, direct) suggests first generation antipsychotics did not improve rate of relapse over placebo.** |
| **Relapse prevention** | |
| Three RCTs compared FGA with placebo (over 1-2 years). Medications assessed included (but were not limited to) fluphenazine, pimozine, and flupenthixol decanoate.<br>*Trend benefit of FGA over placebo;*<br>3 RCTs, N = 166, OR = 5.17, 95%CI 0.87 to 30.63, $p$ = 0.07, $I^2$ = 50%, $p$ = 0.14 | |
| **Consistency in results** | Consistent |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |
| **Comparison 3** | **Second generation antipsychotics (SGA) vs. first generation antipsychotics (FGA) for reducing relapse rate.** |
| **Summary of evidence** | **Moderate quality evidence (medium to large samples, consistent, imprecise, direct) suggests second generation antipsychotics were more effective for reducing relapse than first generation antipsychotics, although this finding was not consistent in individual drug comparisons. There was no difference between first and second-generation antipsychotics for rates of discontinuation due to adverse effects.** |
| **Relapse prevention** | |
| 4 RCTs compared SGA with FGA (over 1-2 years). SGA medications included risperidone, amizulpride, olanzapine, clozapine, quetiapine, ziprasidone. FGA medication included haloperidol and chlorpromazine.<br>*Overall small effect favoured SGAs over FGAs for reducing relapse, however subgroup analyses show no significant difference between specific antipsychotics;*<br>Overall SGAs vs. FGAs: 4 RCTs, N = 1,055, OR = 1.47, 95%CI 1.07 to 2.01, $p$ = 0.02, NNT = 10, $I^2$ = 0%, $p$ = 0.53<br>Risperidone vs. haloperidol: 2 RCTs, N = 551, OR = 1.54, 95%CI 0.98 to 2.42, $p$ = 0.06, $I^2$ = 11%, $p$ = 0.29<br>Clozapine vs. chlorpromazine: 1 RCT, N = 143, OR = 0.81, 95%CI 0.24 to 2.78, $p$ = 0.74<br>Haloperidol vs. various SGAs: 1 RCT, N = 361, OR = 1.38, 95%CI 0.71 to 2.69, $p$ = 0.34 | |
| **Risks** | 4 RCTs reported on discontinuation of medication due to adverse |

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| | events. No significant difference between SGA and FGA for rate of discontinuation; Overall SGA vs FGA: OR = 1.23, 95%CI 0.72 to 2.09, *p* = 0.44. Risperidone vs haloperidol: OR = 1.50, 95%CI 0.99 to 2.27, *p* = 0.06. |
| **Consistency in results** | Consistent |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |
| **Comparison 4** | **First generation antipsychotics vs. other FGAs for reducing relapse rate.** |
| **Summary of evidence** | **Low quality evidence (1 very small RCT) is unable to assess differences in relapse prevention.** |
| **Relapse prevention** | |
| One RCT compared pimozine with flupenthixol (over 1 year).<br>*No significant difference between FGAs for relapse rate;*<br>N = 26, OR = 1.00, 95%CI 0.19 to 5.29, *p* = 1.00 | |
| **Consistency in results** | N/A – one trial |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |
| **Comparison 5** | **Medication maintenance vs. guided discontinuation of antipsychotics (various) for reducing relapse rate.** |
| **Summary of evidence** | **Moderate to low quality evidence (small sample, imprecise, direct) suggests maintenance of medication may be more effective for reducing rate of relapse than discontinuation.** |
| **Relapse prevention** | |
| 1 RCT compared medication maintenance with guided discontinuation, where dosage was gradually tapered until suspended. Medications included risperidone, olanzapine, quetiapine, clozapine and zuclopenthixol.<br>*A medium-sized effect of reduced relapse rate with maintenance of treatment than discontinuation of treatment;*<br>N = 128, OR = 2.91, 95%CI 1.33 to 6.37, *p* < 0.01<br>No difference in number of days confined to bed WMD = -23.31 days, 95%CO -65.71 to -25.09, *p* = | |

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| 0.38. | |
| **Consistency in results** | N/A – one trial |
| **Precision in results** | Imprecise for relapse rate, unable to assess bed days. |
| **Directness of results** | Direct |

*Correll CU, Galling B, Pawar A, Krivko A, Bonetto C, Ruggeri M, Craig TJ, Nordentoft M, Srihari VH, Guloksuz S, Hui CLM, Chen EYH, Valencia M, Juarez F, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, Marcy P, Addington J, Estroff SE, Robinson J, Penn D, Severe JB, Kane JM*

## Comparison of early intervention services vs treatment as usual for early-phase psychosis: A systematic review, meta-analysis, and meta-regression

**JAMA Psychiatry 2018; 75: 555-65**

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| **Comparison** | **Integrated early intervention services specifically designed for people with early-phase psychosis (pharmaceutical and psychosocial such as case management, psychotherapy, supported employment and education, and family support) vs. treatment as usual. Mean trial duration = 16.2 months (range 9-24 months).** |
| **Summary of evidence** | **Moderate to high quality evidence (large samples, mostly consistent, precise, indirect) finds small effects of fewer relapses and hospitalisations and less all-cause treatment discontinuation with early intervention services. These effects were similar across most time points (6, 9-12, and 18-24 months). There were few moderating variables. Studies including fidelity monitoring had fewer hospitalisations than those without fidelity monitoring. Larger study sample size was associated with lower hospitalisation risk.** |
| **Hospitalisation and relapse** | |

*A small, significant effects of fewer hospitalisations and relapses with early intervention services;*

At least one hospitalisation: 10 RCTs, N = 2,105, RR = 0.74, 95%CI 0.61 to 0.90, $p = 0.003$, $I^2 = 47\%$, $p = 0.047$

Number of hospitalisations: 8 RCTs, N = 1,412, SMD = -0.17, 95%CI -0.31 to -0.03, $p = 0.018$, $I^2 = 35\%$, $p = 0.157$

Duration of hospitalisation: 6 RCTs, N = 1,107, SMD = -0.17, 95%CI -0.28 to -0.05, $p = 0.006$, $I^2 = 0\%$, $p = 0.470$

Relapse: 7 RCTs, N = 1,275, RR = 0.71, 95%CI 0.53 to 0.93, $p = 0.014$, $I^2 = 37\%$, $p = 0.143$

In subgroup analyses, the only significant between-subgroup difference was that studies including fidelity monitoring had fewer hospitalisations vs. tau than those without fidelity monitoring (RR = 0.88 vs. 0.50, $p = 0.001$). Meta-regression showed larger study sample size was associated with lower hospitalisation risk (coefficient = 0.001, $p = 0.002$).

There were no moderating effects of region, blinding, type of psychosocial component (family therapy, crisis response, social skills, vocational), number of sites, duration of treatment, number of treatment components, ratio of number of visits in intervention vs. control groups, study risk of bias, diagnosis, baseline symptoms and functioning, age, gender, duration of treated or untreated psychosis, prior antipsychotic treatment, attrition rates.

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| **Risks** | There was less all-cause treatment discontinuation with early intervention services. |
| **Consistency in results** | Consistent, apart from at least one hospitalisation. |
| **Precision in results** | Precise |
| **Directness of results** | Indirect (mixed interventions combined). |

*Kirson NY, Weiden PJ, Yermakov S, Huang W, Samuelson T, Offord SJ, Greenberg PE, Wong BJO*

**Efficacy and Effectiveness of Depot Versus Oral Antipsychotics in Schizophrenia: Synthesizing Results Across Different Research Designs**

**Journal of Clinical Psychiatry 2013, 74(6): 568-575**

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| **Comparison** | **Depot antipsychotics vs. oral antipsychotics.** |

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| **Summary of evidence** | **Moderate to high quality evidence from observational studies (large samples, some inconsistency, precise, direct) suggests a small effect of fewer hospitalisations or relapses in people receiving depot antipsychotics vs. oral antipsychotics, however the result was not significant in the analysis of RCTs.** |
| **Hospitalisation and relapse rates** | |
| *Meta-analyses of observational studies showed a small to medium-sized advantage for depot formulations;*<br>4 prospective studies, N = 3,747, RR = 0.62, 95%CI 0.48 to 0.81, $p < 0.001$, $I^2 = 65.5\%$<br>4 retrospective studies, N = 1,219, RR = 0.56, 95%CI 0.44 to 0.71, $p < 0.001$, $I^2 = 19.4\%$<br>RR reduced to 0.55 ($p > 0.05$) when 2 prospective studies reporting discontinuation as the primary outcome were excluded.<br>RR increased to 0.62 ($p < 0.05$) when 1 retrospective study reporting discontinuation as the primary outcome was excluded.<br>No changes were observed when results were adjusted for mean study duration (21.3 months).<br>*Meta-analysis of RCT shows no differences between groups;*<br>5 RCTs, N = 3,348, RR 0.89, 95%CI 0.64 to 1.22, $p = 0.416$, $I^2 = 85.8\%$<br>Results were similar excluding 1 RCT reporting discontinuation as the primary outcome.<br>RR reduced to 0.74 ($p > 0.05$) when results were adjusted for mean study duration (21.3 months). | |
| **Risks** | No differences in the number of discontinuations (assumed to be due to adverse events). |
| **Consistency in results** | Inconsistent for RCT and prospective studies, consistent for retrospective studies. |
| **Precision in results** | Imprecise for RCT, precise for observational studies. |
| **Directness of results** | Direct for all except adverse events. |

*Kishi T, Ikuta T, Matsui Y, Inada K, Matsuda Y, Mishima K, Iwata N*

**Effect of discontinuation v. maintenance of antipsychotic medication on relapse rates in patients with remitted/stable first-episode psychosis: a meta-analysis**

**Psychological Medicine 2019; 49: 772-9**

# Treatments for relapse prevention

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| **Comparison** | **Discontinuating antipsychotics abruptly vs. gradual tapering off over ~3 months after remittance of a first-episode of psychosis.**<br>**Mean study duration was 18.6 months.** |
| **Summary of evidence** | **Moderate to high quality evidence (medium to large sample, consistent, some imprecision, direct) finds gradual tapering off antipsychotics over 3 months after remittance of a first-episode of psychosis results in fewer relapses for up to 2 years than abrupt discontinuation. However, tapering results in more adverse effects.** |
| **Relapse** | |
| 10 RCTs, N = 776<br>*The maintenance group experienced significantly fewer relapses at all time points except 1 month;*<br>1 month: 6 RCTs, N unclear, RR = 0.55, 95%CI 0.21 to 1.41, $p = 0.21$, $I^2 = 0\%$, $p = 0.46$<br>2 months: 6 RCTs, N unclear, RR = 0.49, 95%CI 0.29 to 0.85, $p = 0.01$, $I^2 = 0\%$, $p = 0.49$<br>3 months: 6 RCTs, N unclear, RR = 0.46, 95%CI 0.30 to 0.70, $p = 0.0002$, $I^2 = 0\%$, $p = 0.84$<br>6 months: 6 RCTs, N unclear, RR = 0.55, 95%CI 0.42 to 0.72, $p < 0.00001$, $I^2 = 0\%$, $p = 0.51$<br>9 months: 6 RCTs, N unclear, RR = 0.48, 95%CI 0.32 to 0.62, $p = 0.0002$, $I^2 = 44\%$, $p = 0.11$<br>12 months: 10 RCTs, N = 739, RR = 0.47, 95%CI 0.35 to 0.70, $p < 0.00001$, $I^2 = 31\%$, $p = 0.16$<br>18-24 months: 4 RCTs, N unclear, RR = 0.57, 95%CI 0.41 to 0.80, $p = 0.001$, $I^2 = 43\%$, $p = 0.16$<br>Authors report there was significant publication bias for the 12-month outcome<br>There were no moderating effects of study size, publication year, study duration, sex, age, duration of illness, or antipsychotic dose at baseline. | |
| **Risks** | The maintenance group was associated with higher discontinuation due to adverse events. |
| **Consistency in results** | Consistent |
| **Precision in results** | Precise, apart from 1 and 2 months. |
| **Directness of results** | Direct |

*Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU*

## Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials

**Schizophrenia Bulletin 2014; 40(1): 192-213**

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| **Comparison** | **Long-acting injectable antipsychotics vs. oral antipsychotics.** |
| **Summary of evidence** | **Moderate to high quality evidence (large samples, precise, some inconsistency, direct) suggests no differences in relapse rates in people receiving long-acting injectable antipsychotics vs. oral antipsychotics.** |

**Relapse rates**

*Overall, there were no differences in relapse rates in patients receiving long-acting injectable antipsychotics vs. oral antipsychotics;*

21 RCTs, N = 4,950, RR = 0.93, 95%CI 0.80 to 1.08, $p = 0.35$, $I^2 = 58\%$, $p = 0.0005$

Subgroup analyses showed first generation long-acting injectable antipsychotics, and those published ≤1991 were superior to oral antipsychotics. Authors suggest these results may be due to publication bias or changes in the way relapse has been defined over time.

No differences between groups for other injectable antipsychotics vs. oral antipsychotics.

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| **Risks** | No differences in the number of discontinuations due to adverse events. |
| **Consistency in results** | Inconsistent for overall analysis, consistent for subgroup analyses. |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

*Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU*

## Long-Acting Injectable versus Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-Analysis of Mirror-Image studies

**The Journal of Clinical Psychiatry 2013; 74(10): 957-965**

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| **Comparison** | **Long-acting injectable antipsychotics vs. oral antipsychotics in mirror-image studies.** |
| **Summary of evidence** | **Moderate to high quality evidence from mirror-image studies (large sample, precise, inconsistent, direct) suggests fewer hospitalisations when people were receiving long-acting injectable antipsychotics compared to when they were receiving oral antipsychotics.** |
| **Hospitalisations** | |
| *A medium-sized effect showed long-acting injectable antipsychotics were superior over oral antipsychotics in preventing hospitalisation;*<br>16 mirror-image studies, N = 4,066, RR = 0.43, 95%CI 0.35 to 0.53, $p < 0.0001$, $I^2 = 87.6\%$, $p < 0.001$<br>Results were similar when analyzing data separately from first-generation antipsychotic studies, risperidone studies, older or newer studies, studies with large or small samples, studies from the U.S. or Europe, studies sponsored or not sponsored by industry, studies that included or did not include dropouts. Heterogeneity was high for all of these subgroup analyses.<br>Note: mirror-image studies compare periods of oral antipsychotic versus long-acting injectable antipsychotic treatment in the same patients. All studies switched from oral to injectable. | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

*Kishimoto T, Agarwal V, Kishi T, Leucht S, Kane JM, Correll CU*

## Relapse prevention in schizophrenia: A systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics

**Molecular Psychiatry 2013; 18: 53-66**

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| **Comparison** | **Second generation vs. first-generation antipsychotics over 6 months of treatment.** |

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| **Summary of evidence** | **Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests a small effect of reduced risk of relapse in people taking second-generation antipsychotics. They may also be superior for tolerability.** |
| **Relapse rates** | |
| *A small effect of reduced relapse risk with second generation antipsychotics;*<br>23 RCTs, N = 4,504, RR = 0.80, 95%CI 0.70 to 0.91, $p = 0.0007$, $I^2 = 37\%$, $p = 0.04$<br>Second generation antipsychotics were also superior regarding treatment failure and hospitalisation rates. | |
| **Risks** | Second generation antipsychotics showed trend-level superiority for dropout owing to intolerability. |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

*Land R, Siskind D, McArdle P, Kisely S, Winckel K, Hollingworth SA*

**The impact of clozapine on hospital use: a systematic review and meta-analysis**

**Acta Psychiatrica Scandinavica 2017; 135: 296-309**

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| **Comparison** | **Clozapine vs. any other antipsychotic.** |
| **Summary of evidence** | **Moderate to high quality evidence (large sample, precise, some inconsistencies and indirectness) suggests a small effect of a reduced risk of hospitalisation with clozapine compared to other antipsychotics.** |
| **Hospitalisation rates** | |

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| *A significant, small effect of fewer hospitalisations with clozapine;*<br>22 studies, N = 44,718, RR = 0.74, 95%CI 0.69 to 0.80, $p < 0.001$<br>There were no moderating effects of study design (RCT or observational), control antipsychotic class (first or second generation), study duration, study year, sample diagnosis (treatment-resistant schizophrenia) or control antipsychotic (risperidone, quetiapine or olanzapine), apart from no differences in hospitalisation rates when clozapine was compared to haloperidol. |

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| **Risks** | Not reported. |
| **Consistency in results** | Authors report there were some inconsistencies in the results. |
| **Precision in results** | Precise |
| **Directness of results** | Indirect for overall analysis, direct for subgroup analyses of individual antipsychotics. |

*Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, Davis JM*

**Maintenance treatment with antipsychotic drugs for schizophrenia**

**Cochrane Database of Systematic Reviews 2012; Issue 5. Art. No.: CD008016. DOI: 10.1002/14651858.CD008016.pub2**

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| **Comparison** | **Antipsychotics vs. placebo.** |
| **Summary of evidence** | **Moderate to high quality evidence (large samples, precise, direct, inconsistent) suggests a medium-sized effect of fewer relapses in people receiving antipsychotics, although antipsychotics resulted in more weight gain, movement disorders and sedation.** |

| **Relapse rates** |
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| *A medium-sized effect of reduced relapse rates across all trial durations (5 to 13 months) in people receiving antipsychotics;*<br>62 RCTs, N = 6,392, RR = 0.35, 95%CI 0.29 to 0.41, $p < 0.05$<br>*There were also fewer aggressive acts in the antipsychotic group;*<br>5 RCTs, RR = 0.27, 95%CI 0.15 to 0.52, $p < 0.05$ |

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| Meta-regression showed the relapse rate effect size increased with increasing study length.<br>Subgroup analyses showed depot preparations reduced relapse more than oral drugs, and unblinded trials reported greater effects than blinded trials.<br>No differences in effect size were reported for number of episodes, whether patients were in remission, abrupt or gradual withdrawal of treatment, length of stability before trial entry, first generation vs. second generation drugs, and allocation concealment method. | |
| **Risks** | There was more weight gain, movement disorders, and sedation with antipsychotics. |
| **Consistency in results** | Authors report substantial heterogeneity which was usually a result of variation in degree of difference rather than in direction of effect. |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

*Sampson S, Mansour M, Maayan N, Soares-Weiser K, Adams CE*

**Intermittent drug techniques for schizophrenia**

**Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD006196. DOI: 10.1002/14651858.CD006196.pub2**

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| **Comparison** | **Antipsychotic use only during periods of incipient relapse or symptom exacerbation (intermittent therapy) vs. continuous treatment (maintenance therapy).** |
| **Summary of evidence** | **Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests intermittent therapy is less effective than maintenance therapy for reducing relapses.** |
| **Relapse and hospitalisation rates** | |
| *Medium-sized effect of more relapses by 26 weeks with intermittent therapy;*<br>7 RCTs, N = 436, RR = 2.46, 95%CI 1.70 to 3.54, $I^2$ 0%, $p$ = 0.70<br>*Small effect size of more hospitalisations by 26 weeks with intermittent therapy;*<br>5 RCTs, N = 626, RR = 1.65, 95%CI 1.33 to 2.06, $I^2$ 0%, $p$ = 0.63 | |

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| **Risks** | No significant differences in tardive dyskinesia with intermittent therapy vs. maintenance therapy. |
| **Consistency in results** | Consistent |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |

*Thompson A, Winsper C, Marwaha S, Haynes J, Alvarez-Jimenez M, Hetrick S, Realpe A, Vail L, Dawson S, Sullivan SA*

**Maintenance antipsychotic treatment versus discontinuation strategies following remission from first episode psychosis: Systematic review**

**BJPsych Open 2018; 4: 215-25**

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| **Comparison** | **Maintenance vs. discontinuaton of antipsychotics following remission from a first-episode of psychosis.** |
| **Summary of evidence** | **Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests relapse and rehospitalisation rates were higher after discontinuation of antipsychotics in people in remission following a first-episode of psychosis. Relapse rates were higher in studies with a short follow-up (<1 year) a non-targeted or non-intermittent discontinuation strategy, a lower relapse threshold, a smaller sample size, and in samples of patients with drug or alcohol dependency.** |

**Relapse and hospitalisation**

*Relapse rates were higher in the discontinuation group;*

7 RCTs, N = 520, RD = 0.26, 95%CI 0.18 to 0.34, $p < 0.05$, $I^2 = 51.2\%$, $p = 0.056$

Discontinuation = 53%, Maintenance = 19%

*Hospitalisations were higher in the discontinuation group;*

5 RCTs, N = 372, RD = 0.12, 95%CI 0.05 to 0.20, $p = 0.002$, $I^2 = 60\%$, $p = 0.042$

Discontinuation = 22%, Maintenance = 11%

Subgroup analyses showed relapse rates were higher in studies with a shorter follow-up period (<1

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| year), a non-targeted or non-intermittent discontinuation strategy, a lower relapse threshold, a smaller sample size, and in samples with patients with drug or alcohol dependency. | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Unable to assess; RDs not standardised |
| **Directness of results** | Direct |

*Uchida H, Suzuki T, Takeuchi H, Arenovich T, Mamo DC*

## Low Dose vs Standard Dose of Antipsychotics for Relapse Prevention in Schizophrenia: Meta-analysis

**The Lancet 2012; 379: 2063-2071**

View review abstract online

| | |
|---|---|
| **Comparison** | **Low dose (50% to < 100% daily defined dose) or very low dose (< 50% daily defined dose) antipsychotics vs. standard dose antipsychotics.** |
| **Summary of evidence** | **Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a small to medium-sized effect of fewer relapses in people receiving standard dose antipsychotics compared to people receiving very low dose antipsychotics, although standard dose antipsychotics resulted more dropouts due to side effects. No differences were reported in relapses or side effects when low dose (50 to < 100%) was compared to standard dose.** |

**Relapse rates**

*A small to medium-sized effect of superior efficacy in standard dose group vs. very low-dose group;*

13 RCTs overall, N = 1,395

Relapse: 6 RCTs, N = 386, RR = 2.75, 95%CI 1.56 to 4.84, $p = 0.0005$, $I^2 = 59\%$, $p = 0.03$

Treatment failure: 6 RCTs, N = 386, RR = 1.24, 95%CI 1.02 to 1.52, $p = 0.03$, $I^2 = 34\%$, $p = 0.18$

Hospitalisation: 5 RCTs, N = 305, RR = 2.21, 95%CI 1.16 to 4.23, $p = 0.02$, $I^2 = 0\%$, $p = 0.64$

No significant differences were reported between low dose and standard dose for any parameter.

| | |
|---|---|
| **Risks** | Less dropouts due to side effects in the very low dose group vs. standard dose. No differences in dropout rates due to adverse events between standard dose and low dose. |
| **Consistency in results** | Inconsistent for relapse and dropout rates, consistent for treatment failure and hospitalisation. |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |

## Explanation of acronyms

CI = confidence interval, FEP = first-episode psychosis, FGA = first generation antipsychotics, $I^2$ = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NNT/B = number needed to treat to benefit, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RD = risk difference, RR = relative risk, SGA = second generation antipsychotics, vs. = versus, WMD = weighted mean difference



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## Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[15].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[15].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.



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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. $I^2$ is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. $I^2$ can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[15];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[16].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.



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